Remarks

In response to the Notice of Non-Compliant Amendment, Applicants have listed all pending claims with showing of changes in each amended claim.

Claims 1, 5-11, and 19-21 are pending, and new claims 30-38 have been added. By this amendment, claims 2 and 22-29 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the canceled claims in a divisional or continuation application(s).

Applicants have amended claim 1 by reciting "wherein said water soluble carrier is polyethylene glycol 8000 (PEG 8000)." This amendment is supported at least by Examples 1 and 2 of the specification. Applicants have also amended claims 5, 8, 20, and 21 to correct typographic errors. In addition, Applicants have amended claims 5-10 to make them dependent from claim 1, instead of from now-canceled claim 2.

Applicants have added new claims 30-38. These claims are supported at least by original claims 1, 2 and 8-10, and Examples 1-2 and page 8 of the specification.

Furthermore, Applicants have amended pages 3 and 11 of the specification to correct typographic errors.

Applicants respectfully submit that the amendments to the specification and claims do not introduce new matter. Accordingly, entry of these amendments is respectfully requested.

Objection to Disclosure

The Office Action mailed September 30, 2003 (hereinafter "the Office Action") objects to the specification for certain informalities. Applicants have amended the specification as suggested by the Examiner, thereby obviating the objection. Reconsideration and withdrawal of the objection are, therefore, respectfully requested.

Objection to the Claims

On page 3, the Office Action objects to claims 5, 8, 20, 21 and 24-27 for informalities. Applicants have canceled claims 24-27, thereby rendering the objection of these claims moot. In addition, Applicants have amended claims 5, 8, 20, and 21 to correct spelling and punctuation errors. Applicants believe that these amendments overcome the Examiner's objection. Accordingly, reconsideration and withdrawal of the objection to claims 5, 8, 20, and 21 are respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

On pages 2-3, the Office Action rejects claims 1, 2, 5, 7-11 and 19-29 under 35 U.S.C. §112, first paragraph, as failing to satisfy the written description requirement. Specifically, the Office Action contends that "[t]he original disclosure contains no indication that Applicants contemplated that HIV protease inhibitors in general, or that specific HIV protease inhibitors other than ABT-538, should be in an amorphous form." Applicants respectfully traverse the rejection.

Applicants have canceled claims 2 and 22-29, thereby rendering the rejection of these claims moot.

Applicants respectfully submit that claims 1, 5, 7-11, and 19-21 satisfy the written description requirement. Example 1 of the specification describes the process of preparing a solid dispersion of ABT-538 (ritonavir), in which ABT-538 was first dissolved in ethanol in a flask, heated to 75°C, and then PEG was added with continual swirling until the PEG melted. The flask was then attached to a rotary evaporator, immersed in a 75°C water bath under vacuum for 15 minutes to remove ethanol. Residual ethanol was removed by drying at room temperature for 6 hours and under vacuum overnight. This procedure produced the amorphous form of ABT-538. Because solid dispersions of ABT-378 and nelfinavir can be similarly prepared, one of ordinary skill in the art would appreciate that ABT-378 and nelfinavir can also be in the amorphous form in these solid dispersions. Accordingly, Applicants respectfully submit that one of ordinary skill in the art would believe that, at the time the present application was filed, Applicants had possession of the claimed invention.

Based on the foregoing, Applicants respectfully submit that claims 1, 5, 7-11 and 19-21 satisfy the written description requirement. Reconsideration of the §112 rejection of claims 1, 5, 7-11 and 19-21 is, therefore, respectfully requested.

On page 3, the Office Action rejects claims 22-29 as being drawn to dispersions generally, rather than requiring solid dispersions. Although Applicants disagree with the Examiner, Applicants have canceled claims 22-29, thereby rendering the rejection of these claims moot.

Rejections under 35 U.S.C. §102(b)

On pages 3-4, the Office Action rejects claims 1, 2, 5 and 11 under 35 U.S.C. §102(b) as being anticipated by Aungst *et al.* (Int. J. Pharmaceutics, Vol 156, pages 79-88) (hereinafter "Aungst I"). Applicants respectfully traverse the rejection.

Applicants have canceled claim 2 without prejudice or disclaimer, thereby rendering the rejection of claim 2 moot.

The legal standard for anticipation is that a claim is anticipated only when the alleged prior art reference discloses each and every element of the claim. Claim 1 claims a "pharmaceutical composition comprising a solid dispersion of an HIV protease inhibitor or a combination of HIV protease inhibitors in a water soluble carrier wherein said water soluble carrier is polyethylene glycol 8000 (PEG 8000) and wherein the HIV protease inhibitor or the combination of HIV protease inhibitors is in amorphous form in the dispersion."

Aungst I does not teach the use of PEG 8000. Moreover, for the reason set forth below, Aungst I does not teach the use of the amorphous form of an HIV protease inhibitor. Accordingly, Applicants respectfully submit that Aungst I does not teach each and every element of claim 1. Accordingly, Applicants respectfully submit that Aungst I does not anticipate claim 1.

Because claims 5 and 11 depend from claim 1, Applicants also respectfully submit that Aungst I does not anticipate claims 5 and 11 either.

On pages 4-5, the Office Action further rejects claims 1, 2, 5, 9, and 11 under 35 U.S.C. §102(b) as being anticipated by Aungst *et al.* (B.T. Gattetosse, Vol. 87, pages 49-54) (hereinafter "Aungst II"). Applicants respectfully traverse the rejection.

As noted, Applicants have canceled claim 2, thereby rendering the rejection of claim 2 moot.

Like Aungst I, Aungst II does not teach the use of PEG 8000 or the amorphous form of an HIV protease inhibitor. Accordingly, Aungst II does not teach each and every element of claim 1 and, therefore, does not anticipate claim 1. Because claims 5, 9, and 11 depend from claim 1, Applicants respectfully submit that Aungst II does not anticipate these claims either.

On pages 5-6, the Office Action also rejects claims 1, 2, 5, 6, 9, 11, 19, 20, 22, and 23 under 35 U.S.C. §102(b) as being anticipated by Al-Razzak *et al.* (U.S. Patent No. 5,610,193). Applicants respectfully traverse the rejection.

Applicants have canceled claims 2, 22 and 23, thereby rendering the rejection of these claims moot.

Al-Razzak *et al.* does not teach a solid dispersion in which the HIV protease inhibitors(s) is in the amorphous form. Accordingly, like Aungst I and Aungst II, Al-Razzak *et al.* does not teach each and every element of claim 1 and, therefore, does not anticipate claim 1. Because claims 5, 6, 9, 11, 19, and 20 depend from claim 1, Applicants respectfully submit that Al-Razzak *et al.* does not anticipate these claims either.

On pages 4-5, the Office Action contends that because no special steps are taken by Aungst I, Aungst II or Al-Razzak *et al.* to produce HIV protease inhibitors in crystalline form, the HIV protease inhibitors in these cited references are "deemed inherently to be in amorphous form . . ." However, as appreciated by those skilled in the art, the amorphous form is generally less stable than the crystalline form. For instance, Almarsson and Gardner (Exhibit 1) observes:

> Amorphous compounds carry inherent risks due to their physicochemical nature. In addition to being physically meta-stable (ie, prone to physical form changes such as crystallization), amorphous forms are generally less chemically stable in the solid state than the crystalline form. Amorphous compounds also tend to have very low bulk densities, making the materials difficult to isolate and handle. They also exhibit irregular particle properties and their high surface area often results in hygroscopicity (excessive moisture-sorption). These properties, despite presenting a potentially surmountable set of issues in discovery and early development, can cause major challenges in late-stage development. (Page 22, the middle column).

Because of the inherent instability of the amorphous form, Applicants respectfully submit that the HIV protease inhibitors described in the cited references should not be "deemed inherently to be in amorphous form." *See* MPEP 2112 IV ("The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic") (emphasis in original). *See also id.* ("To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'") (Citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)).

In addition, Applicants respectfully submit that because of the differences in the preparation steps, the Office Action has not met satisfy the initial burden to establish that the procedures used in the cited references "necessarily" produce solid dispersions of amorphous HIV protease inhibitors. *See id.* ("In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.") (emphasis in original) (citing *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). For instance, in column 9, lines 41-63, Al-Razzak *et al.* describes:

> In general, the compositions of this invention can be prepared in the following manner. The pharmaceutically acceptable acid or acids are added to the pharmaceutically acceptable organic solvent or mixture of solvents with mixing. Ethanol (dehydrated, USP, 200 proof) can be used as a cosolvent. If an antioxidant is used, it is then added with mixing. Then the HIV protease inhibitor is slowly added with mixing until it is completely dissolved. Lastly, any viscous pharmaceutically acceptable organic cosolvents and/or other additives, such as surfactants, are added with mixing.
>
> The pharmaceutically acceptable adsorbent or mixture of adsorbents is charged into a Hobart mixer and mixed. The above solution is added dropwise to the dry mixture in the Hobart mixer while mixing at slow speed. The mixture is massed until granular.
>
> The granulation is screened through an appropriate sized screen. If ethanol is used as a cosolvent, prior to being filled into capsules, the wet granulation can optionally be dried in a tray dryer or a fluidbed dryer until the loss on drying is not greater than the amount of ethanol originally in the adsorbed solution.

In contrast, Example 1A of the present application describes, as a non-limiting example, that ABT-538 (ritonavir) was first dissolved in ethanol which was then heated to 75°C, and then PEG (or another suitable water soluble carrier or carriers) was added to the hot alcohol solution until the PEG melted. The majority of the ethanol was then removed in 15 minutes using a rotary evaporator at about 75°C, followed by cooling in an ice bath and further drying at room temperature for 6 hours and under vacuum overnight.

Because of the significant differences between Example 1A of the present application and the procedures described in Al-Razzak *et al.*, Aungst I and Aungst II, Applicants respectfully submit that the Office Action has failed to establish a *prima facie* case of anticipation by

inherency. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the inherency rejection of claim 1, 5, 6, 9, 11, 19, and 20.

New Claims 30-38

Applicants have added new claims 30-38. These claims are supported at least by original claims 1, 2 and 8-10, and Examples 1-2 and page 8 of the specification. Applicants respectfully submit that Aungst I, Aungst II and Al-Razzak *et al.*, either individually or in combination, do not teach or suggest claims 30-38. As noted, these cited references neither teach nor suggest amorphous ritonavir. Accordingly, these cited references do not teach or suggest each and every element of claims 30-38. Therefore, Applicants respectfully submit that claims 30-38 are patentable over the cited references. *See* MPEP 2131 ("To anticipate a claim, the reference must each every element of the claim"). *See also* MPEP 2143.03 ("To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art").

Conclusion

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly solicited. Although Applicants believe that the fees paid herewith are correct, the Commissioner is hereby authorized to charge any payment deficiency to deposit account number 01-0025 referring to docket number 6488.US.O2.

Should the Examiner believe that anything further is desired in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' representative designated below.

Respectfully submitted,

Date: August 28, 2006

Xu Zhang
Lim. Rec. No. L0116

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EXHIBIT 1

Novel approaches to issues of developability

Örn Almarsson & Colin R Gardner
TransForm Pharmaceuticals Inc, USA


Considerations of developability, such as 'is the compound drugable', are often left until a lead is selected for trials. Investigating the form and formulation of compounds at the early preclinical stage can save significant costs and time. Here we take a look at how to ensure your candidate is a suitable drug using high-throughput form and formulation technologies.

In recent years, several new technologies have been developed which have enabled great strides in the generation of lead compounds for development into pharmaceuticals. First, the genomic revolution cast a floodlight on the diversity and expression of putative targets for drug discovery. Second, the advent of combinatorial chemistry produced vast libraries from which discovery groups could initiate searches for compounds active at new targets. Third, *in vitro* potency and selectivity assays have become automated with newly available commercial equipment, which is increasingly user-friendly to laboratory personnel. Automation in preclinical research (including metabolic profiling and permeability screening) has facilitated identification of membrane-permeable molecules, the metabolism of which can be characterized at a fairly early stage. These advances were in all cases made possible by high-throughput (HT) methodologies.

Despite this progress, the drug industry finds itself in a productivity crisis as the number of new drugs registered has not kept pace with the increased resource expenditures in discovery. Two elements that exacerbate the issue are the increasing chemical complexity of compounds in discovery and the lack of available technologies to deal with the increased output of compounds downstream of discovery. Increased chemical complexity is a result of advances in genomics and combinatorial chemistry; there are more plentiful targets that require increasingly elaborate molecules to selectively address the intended target. Combinatorial chemistry has led to the generation of compounds that have progressively more challenging properties; an acute lack of water solubility, as well as poor dissolution characteristics, are frequently a problem in early development.

What is developability?

'Developability' refers to the quest for desirable properties beyond the classical focus on potency and selectivity, ie, does a compound have the desirable pharmaceutical properties to make a drug? The key to efficiently traversing the preclinical stage of drug development involves the marriage of classical criteria with consideration of developability. Limitations of developability raise significant hurdles for advancing compounds into the clinic and for this reason, preclinical development is showing signs of becoming a bottleneck. Due to the mounting pressure on development groups to bring challenging compounds forward to proof-of-principle studies in the clinic, new technologies and capabilities are needed to accelerate preclinical evaluation. In order to increase the chances of identifying a compound with suitable physical properties and advancing it to development, HT techniques are now being devised for the preclinical space.

Two questions are beginning to receive attention across the pharmaceutical industry and they provide the focus of this article: Why is consideration of pharmaceutical properties becoming increasingly critical to drug discovery and preclinical development? And, what HT strategies help to address developability at earlier stages, when amounts of test substance are often limiting?

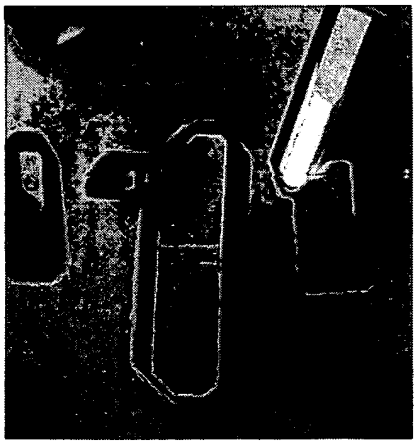

Figure 1. The form of a drug candidate is a critical attribute that determines the physical properties of the compounds and significantly affects pharmaceutical processing, stability and bioavailability.

The importance of physical form

To address the question of why consideration of pharmaceutical properties is becoming increasingly critical to drug discovery and preclinical development, one must consider the importance of physical form (Figure 1). Form determines function; this statement is true in the world of materials in general. For instance, the differences in properties between a crystalline and a non-crystalline (amorphous) compound are easily recognizable in terms of density, hardness, stability to stress, etc. The properties of a drug product are determined by the materials that it contains. Therefore, an active molecule must be converted into a pharmaceutical material in order to make it useful to the patient. Nevertheless, form definition (the selection of the optimal crystal form of a drug substance) and formulation activities to prepare the compound for toxicology and ultimately human studies are sometimes seen as 'necessary evils' in advancing a candidate compound from discovery to clinical development. Due to lack of available material, there is conscious prioritization of its use in the biological assays, pharmacokinetic evaluation and pharmacological studies in animals. Few resources are typically allocated to physical characterization of early stage compounds but, as a consequence of poor definition of the physical nature of the candidate compound, a discovery-to-development transition may stall due to problems with the solid form of the substance and hence the formulation options that are available. Let us consider two issues of developability that are commonly faced in the corridor leading from discovery to early stages of drug development: amorphous materials and insoluble, poorly-absorbed compounds.

Amorphous materials

Discovery programs frequently yield amorphous compounds due to time pressures and the methods used to isolate them on small scales. In addition, lead compounds have evolved in terms of their structural complexity, and hence crystallization is a challenge that often awaits the involvement of pharmaceutical and process chemists. Examples of amorphous compounds that have persisted through development and reached the market are listed in Table 1.

"...a major driver for early consideration of pharmaceutical properties is the mounting formulation challenge in preclinical development."

Amorphous compounds carry inherent risks due to their physicochemical nature. In addition to being physically meta-stable (ie, prone to physical form changes such as crystallization), amorphous forms are generally less chemically stable in the solid state than the crystalline form. Amorphous compounds also tend to have very low bulk densities, making the materials difficult to isolate and handle. They also exhibit irregular particle properties and their high surface area often results in hygroscopicity (excessive moisture-sorption). These properties, despite presenting a potentially surmountable set of issues in discovery and early development, can cause major challenges in late-stage development.

In general, pharmaceutical companies make every effort to avoid committing to the development of an amorphous compound. When sufficient quantities of such a compound become available, development scientists may obtain a crystalline form, the solubility of which can be dramatically (up to orders of magnitude) lower than that of the amorphous form. The decreased solubility frequently compromises or even abolishes oral absorption from the solid-state. This unsatisfying predicament leads to major resource expenditures in formulation development to recover *in vivo* performance. The resulting formulations often do not meet the criteria of chemical stability and processability, and hence the resulting dosage forms may limit the progress of a clinical program. As has already been stated, amorphous forms have, in rare cases, been chosen for development despite the risk of crystallization, an event that could cause a product to fail its critical performance criteria and regulatory specifications. The results of such an occurrence are disastrous for development programs, especially in late-stage trials where the formulation used is that intended for the market.

Insoluble poorly-absorbed compounds

In those cases where a crystal form exists but has poor or non-existent bioavailability, significant effort is often spent finding formulations that improve absorption characteristics. Frequently, an innovator

Drug product	Drug substance	Molecular weight	Therapeutic class and use
Accupril®	Quinapril HCl	439	ACE inhibitor for hypertension
Accolate®	Zafirlukast	576	Leukotriene antagonist for asthma
Viracept®	Nelfinavir mesylate	568	HIV protease inhibitor for AIDS

Table 1. Examples of FDA-approved products based on amorphous drug substances.

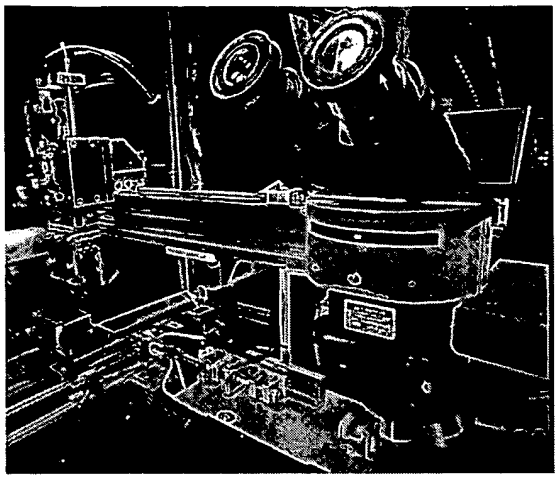

Figure 2. An automated Raman microscope is a central part of high-throughput crystallization, enabling rapid characterization and classification of novel solid forms of drug candidates.

company may be in this situation because a compound that was previously amorphous and well absorbed in early animal studies was converted to a much less bioavailable crystalline state in the development phase. Although oral solutions may overcome poor oral absorption, such an approach is generally not considered ideal due to stability and user acceptance concerns. For instance, taste considerations can adversely affect the progress of a clinical program and marketing groups are usually averse to the idea of an oral solution product as their major marketed dosage. Strategies to improve absorption without resorting to a solution formulation include formation of a salt or the creation of dispersions, both of which aim to increase dissolution rate of the compound, thus enabling improved oral absorption.

Occasionally, suitable salt forms of acidic or basic compounds are not obtained, despite significant efforts in salt selection. Molecular dispersions, such as a solid-solution of drug in a semi-solid matrix or suspensions of nanometer-sized test substance with surfactants and other suspending aids, share some of the same stability risks as amorphous compounds: over time, and generally in an unpredictable fashion, nucleation and/or growth of crystalline particles may take place. As a result, the level of compound solubility or dissolution rate that was previously recorded in the medium is lost with adverse consequences for the bioavailability. The development of dispersions is therefore challenging and risky.

Clearly, a major driver for early consideration of pharmaceutical properties is the mounting formulation challenge in preclinical development. The issues of amorphous compounds and poorly-absorbed crystalline forms raise the specter of increased complexity of dosage form development, which is unpalatable to pharmaceutical companies in an increasingly competitive industry where speed to market is critical. If the issues are not addressed successfully early on in the pre-clinical stage, the compound may fail or become sidelined in order to progress another candidate that satisfies formulation criteria including developability and the desires of marketing groups. Because a compound in the formulation stage is relatively far along in preclinical development, the opportunity costs associated with dropping the compound for lack of ability to formulate (developability) are quite significant.

Form and formulation opportunities

What HT strategies can be brought to bear to address form and formulation (F&F) issues encountered in preclinical drug development? One way to preempt problems of developability without a substantial increase in resources is to apply HT technologies in the following areas:

- Crystallization of amorphous compounds (identification of a stable physical form)
- Salt selection (when salt forms are required to optimize performance)
- Preformulation (solubility, stability and compatibility of crystal forms with potential formulation components)
- Formulation (eg, liquids or suspensions for toxicology and proof-of-principle human studies)

Two major challenges to overcome in the design and implementation of HT F&F technologies are: (i) the need for specialized equipment for dispensing and analysis; and, (ii) the limited availability of test material. On the equipment side, one must be able to handle a range of materials, including non-aqueous, viscous liquids and semi-solid materials and because only a limited selection of commercial equipment to handle such a range of properties simultaneously is available, significant customization is inevitable. Analysis equipment may include sophisticated vision systems and spectroscopic techniques that need to be custom-fitted to allow in-line analysis of crystals or formulations.

The lack of available material is another major impediment to application of HT in discovery or at the discovery-development interface, since at this stage the bulk of a given compound that is advancing toward candidate selection is funneled into animal experiments. It is difficult to justify the cost of scaling up syntheses of discovery phase compounds, most of which will not have much value beyond discovery. Generally, a diversity of molecules is required in the early days to establish the structure-activity relationships and because common intermediates are used to prepare such compounds, the stock of the intermediate at any time is limited. Therefore, in order to move F&F research toward lead optimization support, one must learn how to do more, with less material from the discovery phase. For example, the search for crystal forms and salts of compounds emerging from discovery must rely on automation and miniaturization of crystallization trials. Currently, development chemists may experiment with 1-10 mg per trial on a total budget of 10s to 100s of milligrams. Although material is usually recoverable at a cost in time and effort, the traditional experimentation remains linear in nature. The search for crystal forms in such a linear fashion is time-consuming, and all the while the pressure mounts to test a compound in toxicology and the clinic. The technical solution provided by HT crystallization is the possibility of parallel, miniaturized trials of a

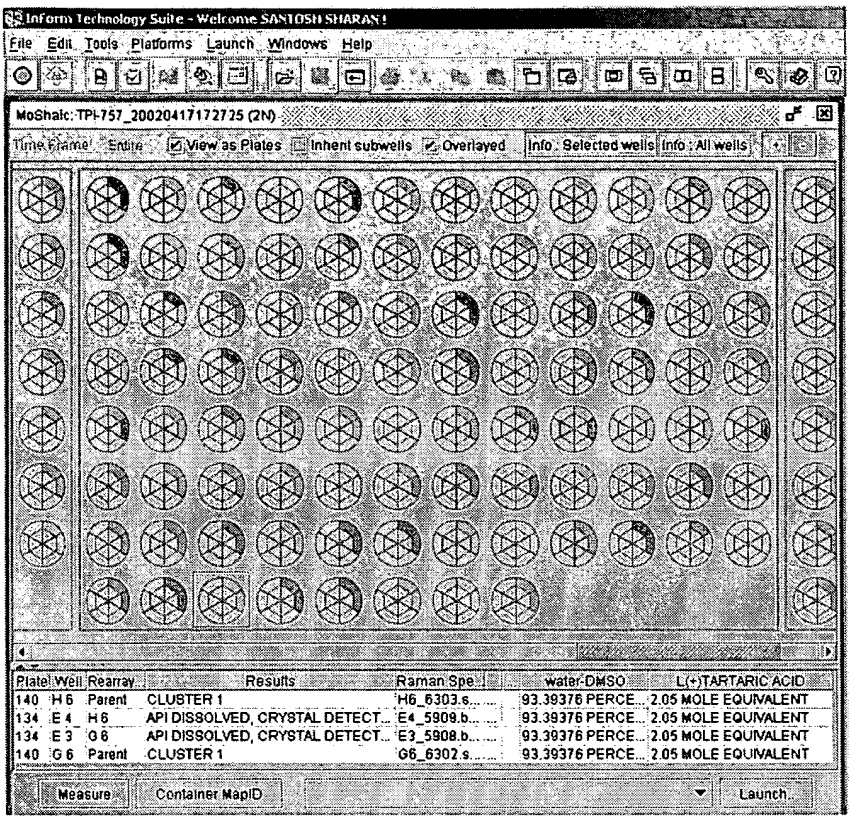

Figure 3. Informatics software allows the analysis of high-throughput F&F screening data to identify leads for preclinical evaluation and dosage form development for clinical studies.

larger experimental space (solvents, combinations, processing parameters, and so on). In order to meaningfully increase the productivity of crystallization efforts, one must be able to conduct parallel experiments at the level of micrograms per trial. In this way, valuable time and material can be saved, while generating useful physicochemical information to support development decisions. For instance, if crystalline forms are found, the program can confidently move forward to assessing their utility.

Even when a crystal form remains elusive, the information from crystallization trials on the compound and some of its congeners may help the medicinal chemists design the optimal compound to advance the program. Also, the inability to crystallize a compound in a large number of parallel trials can sometimes give a scientists working on a program sufficient confidence to use an amorphous form (even though the absence of crystalline material in HT experiments can never disprove the existence of a crystal form entirely). Downstream of discovery, the issue of polymorphism, which is defined as the presence of distinct crystalline forms of a given compound, becomes a technical and regulatory challenge, an important example of which will be provided towards the end of this article. HT crystallization screening provides a way to address polymorphism issues much earlier and can help to avoid late discoveries of polymorphism in pharmaceutical systems.

TransForm HT technology

Through significant investment in automation and informatics, TransForm Pharmaceuticals has developed distinctive F&F HT platforms, including an HT crystallization technology called CrystalMax™, which enables parallel, miniaturized crystallization of compounds in cycles of 1- to 2-weeks (Figures 2 and 3). Iterations are possible, indeed desirable, and a database tracks all transactions relating to every experiment. Visualization and analysis of data from the database is a key feature that enables decision-making regarding form selection. The technology allows design, execution and analysis of thousands of crystallization trials on 100s of micrograms of crystalline material per well in microliter volumes within a 96-well array format. Much of the CrystalMax™ technology platform is custom-made, since off-the-shelf solutions are not considered adequate. For instance, current systems suffer from incompatibilities with handling of a vast variety of volatile organic solvents used to produce crystal diversity. One of many examples of the success of the new platform is shown in a recently published study of the crystal polymorphism of the well-known drug acetaminophen (paracetamol) (Peterson ML *et al*).

FAST™ is an HT technology that was developed to discover novel solution formulations of poorly soluble compounds, either for intravenous or oral use. The technology uses 96-well format to conduct parallel screening of thousands of combinations of semi-aqueous formulations. Another formulation technology, SFinX™, has been developed to discover excipient combinations that dissolve poorly water-soluble compounds for oral delivery. As part of the process, non-aqueous concentrates are presented to an *in vitro* dissolution test in 96-well plates, in order to assess the physical form of the drug that will be produced upon dilution in GI tract. These results can be used to predict impact on oral bioavailability. TransForm is applying the above breakthrough technologies in partnerships with major pharmaceutical companies that have recognized the value of early intervention in the area of F&F.

Pharmaceutical companies are considering their options to enhance efficiency in F&F research, either by expanding their capabilities internally, purchasing tools or by outsourcing HT experimentation with pharmaceutical materials. A handful of technology companies are positioning themselves to provide HT crystallization automation tools (Symyx Technologies, Crystallics, Solvias) in the preclinical space.

Impact points

Increasingly, compounds are stalling in development due to issues of form and formulation, and these problems were likely already evident in the discovery phase. Others experience unanticipated biopharmaceutical problems in development or, worse, on the market. The emerging way to avoid these problems is to conduct miniaturized experiments earlier combined with informatics-aided analyses of solubility, solid form diversity, formulation options and biopharmaceutical data. The vision of cross-correlating physical, chemical and biological information for diverse chemical structures is shared by a number of pharmaceutical companies that operate with ever growing sample collections. At present, the best examples of the value of understanding the nature of compounds are historical ones. The examples chosen come from analysis of the pharmaceutical issues with HIV protease inhibitors.

Many will realize that the tremendous strides made in HIV therapy due to the advent of the protease inhibitors in the mid 1990s would not have occurred without the knowledge and experience gained a half a decade earlier, when several companies were deeply involved in the discovery of renin inhibitors. The latter class of compounds largely comprise peptidomimetics, which are compounds that frequently possess the challenging properties of poor aqueous solubility and metabolic instability toward cytochrome P450 enzymes. These issues are prominent in the HIV protease inhibitor class. The types of marketed formulations in this class illustrate the problems that exist with achieving bioavailability (Table 2). In essence, the oral dosage forms consist of drug in an oily solution within soft gelatin capsules or more water-soluble (and in one case amorphous) salt forms in hard gelatin capsules. There were significant challenges along the way to achieving these formulations. Two examples of high-profile problems relate to saquinavir (Invirase® and Fortovase®) and ritonavir (Norvir®).

"HT crystallization screening provides a way to address polymorphism issues much earlier and can help to avoid late discoveries of polymorphism in pharmaceutical systems."

It is well known that the utility of saquinavir, the first HIV protease inhibitor on the market, was severely impeded by poor bioavailability. Because bioavailility and pharmacokinetics are crucial determinants of the activity of an anti-infective drug, the original formulation, Invirase showed only modest market performance at its peak. Invirase soon became overshadowed by drugs such as ritonavir (Norvir) and indinavir sulfate (Crixivan®) that had better bioavailability. Three years after initial approval, saquinavir was re-introduced in a formulation with six-fold higher oral bioavailability relative to the original product. By extensive F&F effort, the new formulation, Fortovase, was engineered in such a way as to emulsify the drug more effectively in gastric fluid than was possible before. One can surmise that having the better performing formulation at the outset could have enhanced saquinavir's market penetration by mitigating the issue of poor bioavailability of the original formulation.

Ritonavir was originally launched as a semi-solid dosage form, in which the waxy matrix contained dispersed drug in order to achieve acceptable oral bioavailability. In 1998, two years after its introduction, ritonavir exhibited latent crystal polymorphism, which caused the semi-solid capsule formulation of Norvir to be removed from the market. The new drug crystal form did not have sufficient solubility in the formulation and the product therefore began failing dissolution specifications. Knowledge of the crystal form diversity of ritonavir would likely have averted this painful experience. A new formulation was developed; a soft-gelatin capsule containing a liquid excipient mixture in which the new crystal form is soluble.

The storage label for Norvir capsules indicates refrigeration of the drug prior to dispensing to the patient. The same is

HIV Protease	Products	Oral formulation(s)
Saquinavir	Invirase®[1]	Hard gelatin capsule containing the mesylate salt form
Saquinavir	Fortovase®[2]	Soft gelatin capsule containing the free base drug form
Indinavir	Crixivan®	Hard gelatin capsule of the crystalline sulfate salt
Ritonavir	Norvir®	Soft gelatin capsule; oral solution
Amprenavir	Agenerase®	Soft gelatin capsule; oral solution
Nelfinavir	Viracept®	Hard gelatin capsule of the amorphous mesylate salt
Lopinavir	Kaletra®[3]	Soft gelatin capsule; oral solution

[1] Original product.
[2] Improved product with 6-fold bioavailability relative to Invirase®.
[3] Formulated as a fixed-dose combination of Lopinavir with Ritonavir.

Table 2. FDA-approved HIV protease inhibitors.

true for the recent combination protease inhibitor, lopinavir (Kaletra®) (Table 2). The late discovery of crystal polymorphism of ritonavir is another example of a disaster that might have been averted by early HT study of crystal forms of the compound.

Developability moving forward

One can envision a future when the developability of a scaffold or drug class is known well in advance of lead optimization and preclinical research. The key to interfacing early in discovery will be the ability to work with microgram amounts of substance, advanced design of experiments with sophisticated informatics, and high-speed analysis to create valuable information across compound series and even an entire sample collection. Database capture of pharmaceutics from HT experimentation, and the knowledge that will emanate from coupling developability data with biological data, gives rise to boundless possibilities to accelerate drug discovery and development.

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FURTHER INFORMATION

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